Pergamon

Tetrahedron 54 (1998) 2423–2432

TETRAHEDRON

An Efficient Synthesis of the Side Chain Intermediate of BO-2502A, a New 1β-Methyl Carbapenem, *via* Diastereoselective Lactamization as a Key Step

Norikazu Ohtake*, Yasuyuki Imai, and Ryosuke Ushijima

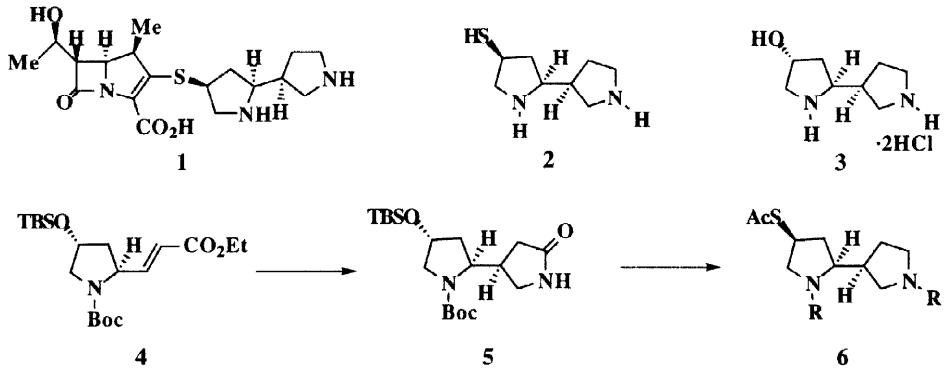
Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd., Okubo 3 Tsukuba 300-26, Japan.

Received 20 October 1997; accepted 24 December 1997

Abstract: The BO-2502A side chain intermediate **3** was prepared *via* the diastereoselective lactamization of the *in situ* prepared amino diacid anhydride **14** as a key step. The diastereoselectivity of this step was found to be 53:1 (96% de).

Introduction

Following the discovery of thienamicyn,[1] 1β-methyl carbapenems were found by Merck scientists[2] to have improved properties including antimicrobial activity and chemical and metabolic stabilities. Since then, many research groups have attempted to develop 1β-methyl carbapenems as second-generation carbapenems. Meropenem,[3] one of the successful 1β-methyl carbapenems, was recently introduced to the market.



In our laboratories, BO-2502A **1**,[4] a new 1β-methyl carbapenem, was identified as a lead compound that possesses improved antibacterial activity against *P. aeruginosa* and a better pharmacokinetic profile than imipenem[5] and meropenem.

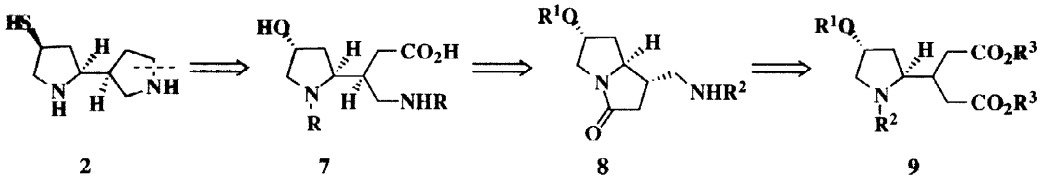
The C-2 side chain **2**, bearing a (3S)-pyrrolidin-3-yl moiety on the C-5 position of the mercaptopyrrolidine ring,[6] was initially prepared as its precursor **6a** (R = *p*-nitrobenzyloxycarbonyl) from the α,β-unsaturated ester **4** *via* pyrrolidone **5**.[4] However, this method was ineffective due to poor diastereoselectivity in the Michael addition of nitromethane to **4**. The necessity for the carbapenem side chain **2** in large quantities prompted us to develop an efficient diastereoselective synthesis of **3**, which is readily converted to **2**. In this paper we describe the results of the diastereoselective synthesis of the side chain intermediate **3** from commercially available (2S, 4R)-L-hydroxyproline.

Results and Discussion

Our synthetic strategy involves the diastereoselective lactamization of symmetric diester **9**, introduction of amine function by Curtius rearrangement of the resulting ester moiety, and direct cyclization of the second pyrrolidine ring from amino acid derivative **7** (see Scheme 1).

0040-4020/98/$19.00
PII: S0040-4020(98)00007-6

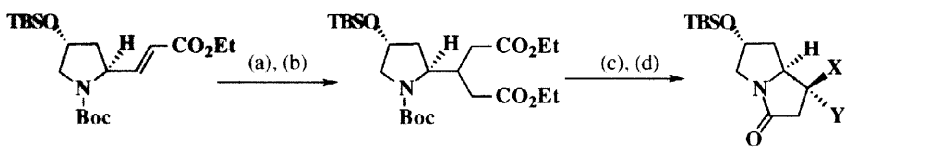
Scheme 1. Retro-synthesis of **2**



2 **7** **8** **9**

First, **11b** was prepared from the α,β-unsaturated ester **4** in good yield by the following method: (1) Michael addition of ethyl malonate to **4**, (2) deethoxycarbonylation under Krapcho's conditions,[7] (3) selective deprotection of the Boc group of **9b** with trifluoroacetic acid (TFA), and (4) lactamization under basic conditions. However, the diastereoselectivity of the lactamization was insufficient (**11b** : **12b** = 1.5 : 1).[8]

Scheme 2. Preparation of the lactmas **11b** and **12b.**



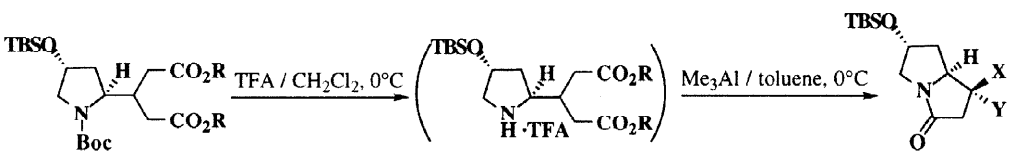
4 **9b**

11b : X = H, Y = CH_2CO_2Et

12b : X = CH_2CO_2Et, Y = H

Reagents : (a) 60% NaH, $CH_2(CO_2Et)_2$, 50°C THF, (b) NaCl, DMSO, 160°C, (c) TFA, CH_2Cl_2, 0°C, (d) NEt_3, toluene, 50°C.

Table 1. Diastereoselectivity of Weinreb lactamization of **10a-d.**

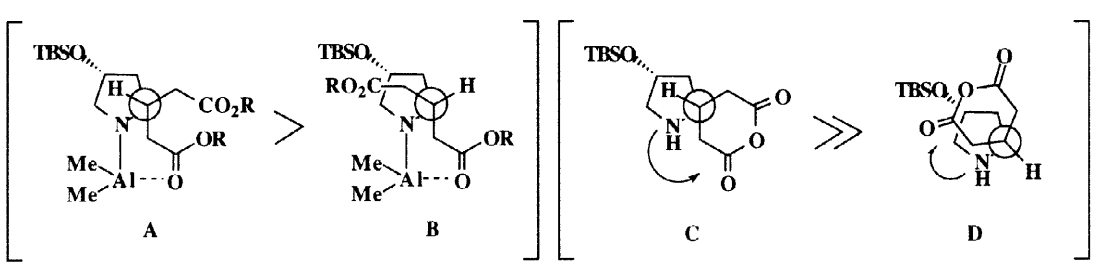


9 **10**

11 : X = H, Y = CH_2CO_2R

12 : X = CH_2CO_2R, Y = H

	Substrates		Products		
Run	9	R	Ratio (**11**/**12**)	de (%)	Yield (%) of **11** and **12**
1	a	Me	1.5	20	67
2	b	Et	2	33	80
3	c	*ic*-Pr	3.5	55	79
4	d	Bn	7.2	76	86



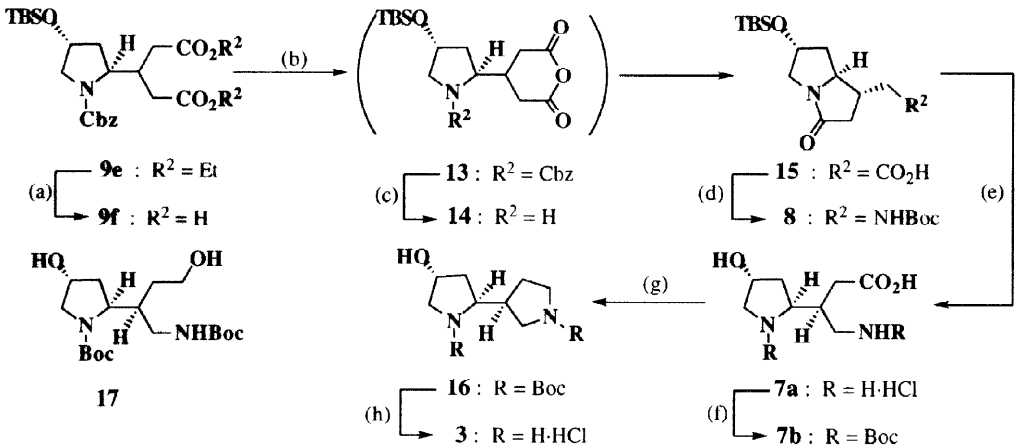
A **B** **C** **D**

Treatment of the amine intermediates **10a–d**, derived from **9a–d**, with $AlMe_3$ (Weinreb lactamization)[9]

afforded lactams **11a–d** and **12a–d**, with varying diastereoselectivity. The best selectivity (**11d** : **12d** = 7.2 : 1, 76% de) was achieved using the benzyl ester **9d** as shown in Table 1. The improved diastereoselectivity could be explained by assuming that the transition state **A** is sterically more favorable than **B**.

On the basis of the above results, we envisioned the amino diacid anhydride **14**, which would react intramolecularly to afford carboxylic acid **15** diastereoselectively *via* the more favorable transition state **C**.

Scheme 3. Diastereoselective synthesis of the key intermediate **3**.



Reagents: (a) 1N NaOH, EtOH, (b) DCC, THF, (c) 10% Pd-C, H_2, THF, (d) $(PhO)_2PON_3$, NEt_3, *tert*-BuOH, 70°C, (e) conc HCl, 100°C, (f) Boc_2O, Na_2CO_3, dioxane-H_2O, (g) BH_3·SMe_2, THF, 40°C, (h) HCl-MeOH.

For the preparation of **14**, *N*-benzyloxycarbonyl-protected dicarboxylic acid **9f** was used as a precursor. The dicarboxylic acid **9f** was reacted with DCC in THF to give anhydride **13**, which was subsequently treated with 10% Pd-carbon under hydrogen atmosphere without isolation. The lactamization proceeded smoothly to produce the desired carboxylic acid **15** diastereoselectively (96% de) in excellent yield. [10, 11] The Curtius rearrangement of **15** with diphenylphosphoryl azide under the Shioiri's condition[12] gave the lactam **8** (>99% de) in 63% yield, which was identical to the lactam **8** derived from the pyrrolidone **5**.[4, 6] The lactam **8** was hydrolyzed under acidic conditions to give the amino acid **7a**, which was protected with di-*tert*-butyl dicarbonate, affording **7b**. At first, cyclization of the second pyrrolidine ring was planed *via* the selective tosylation of diol **17** derived from **7b**. However, we found that the direct reductive cyclization of **7b** to bis pyrrolidine **16** was effected by BH_3·SMe_2. The bis pyrrolidine **16** was easily converted to thioacetate **6b** (R = Boc) by Mitsunobu reaction.[13] Deprotection of **16** with methanolic hydrogen chloride gave the desired side chain intermediate **3** as a white crystalline solid. Transformation of **3** to thioacetate **6a** was reported previously.[4]

In summary, we succeeded in the diastereoselective synthesis of the side chain intermediate **3** from (2S,4R)-L-hydroxyproline *via* the stereoselective lactamization of the *in situ*-prepared amino diacid anhydride **14** (96% de) by 1,2-asymmetric induction as a key step.

Experimental

General methods. Melting points were measured on a Yanaco MP micromelting point apparatus and were not corrected. The ^1H NMR spectra were recorded on a Varian GX-300 spectrometer with tetramethylsilane (TMS) or 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard. ^{13}C NMR spectra were recorded on a JEOL EX-400. IR absorption spectra were recorded with Horiba FT-200

spectrometer. Optical rotations were measured with Jasco DIP-370 polarimeter. Mass spectra (MS) were measured on a JEOL JMS-SX102A spectrometer. TLC was performed with Merck Kieselgel F_{254} precoated plates. The silica gel used for column chromatography was WAKO gel C-300.

Diethyl 3-[(2S,4R)-*N*-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl] glutarate 9b.

To a suspension of 60% NaH (1.22 g, 30.4 mmol) in THF (80 ml) was added diethyl malonate (4.61 ml, 30.4 mmol) at 4 °C, and the mixture was stirred for 30 min at room temperature. To this mixture was added **4** (7.4 g, 15.2 mmol) in THF (20 ml) and the resulting mixture was further stirred overnight at 50 °C. The reaction mixture was quenched by adding saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and evaporated under reduced pressure. To the residue in DMSO (50 ml) were added NaCl (890 mg, 15.2 mmol) and H_2O (0.55 ml, 30.4 mmol), and the mixture was heated at 160 °C for 1hr. The mixture was cooled to room temperature, poured into H_2O, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification of the residue by silica gel column chromatography yielded **9b** (7.9 g, 88 %), $[\alpha]_D^{20}$ –23.2 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 1739, 1695, 1392 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.85 (9H, s), 1.25 (6H, t, J = 7.2 Hz), 1.48 (9H, brs), 1.71 (1H, m), 1.90 (1H, m), 2.03~2.45 (4H, m), 2.82~3.22 (2H, m), 3.35~3.67 (1H, m), 3.97~4.25 (5H, m), 4.30 (1H, br); FAB-HRMS calcd for $C_{24}H_{46}NO_7Si$ $(M+H)^+$: 488.3043. Found: 488.3028.

Diethyl 3-[(2S,4R)-*N*-benzyloxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl] glutarate 9e.

9e was prepared as described for the preparation of **9b**, $[\alpha]_D^{20}$ –27.2 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 1738, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.83 (9H, s), 1.15~1.28 (6H, m), 1.78 (1H, m), 1.90 (1H, m), 2.12~2.42 (4H, m), 2.95~3.15 (1H, m), 3.24 (1H, dd, J = 3.8, 11.7 Hz), 3.45~3.70 (1H, m), 3.95~4.18 (5H, m), 4.34 (1H, br), 5.03~5.25 (2H, m), 7.25~7.43 (5H, m); FAB-HRMS calcd for $C_{27}H_{44}NO_7Si$ $(M+H)^+$: 522.2887. Found: 522.2871.

(4S,5S,7R)-7-*tert*-Butyldimethylsilyloxy-4-ethoxycarbonylmethyl-2-oxo-1-azabicyclo [3,3,0]octane 11b and its **(4R)-isomer 12b.**

Experimental procedure for Table 1, Run 2 is described as a representative procedure as follows.

To a solution of **9b** (225 mg, 0.46 mmol) in CH_2Cl_2 (3 ml) was added trifluoroacetic acid (3 ml) and the mixture was stirred for 1hr at 4 °C. The reaction mixture was concentrated under reduced pressure. Toluene (3 ml) was added to the residue and the mixture ws concentrated under reduced pressure. To a solution of the residue in toluene (8 ml) was added a 2.0 M of trimethylaluminum in toluene (0.47 ml, 0.94 mmol) at 0 °C. After the mixture was stirred for 30 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with EtOAc. The organic layer was washed with 1N NaOH, H_2O, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **11b** (67 mg, 43%), **12b** (29 mg, 18%), and the mixture of **11b** and **12b** (30 mg, 19%), [HPLC analysis: column, YMC A-001 (S-5, 120A SIL); detection, 210 nm; eluent, 50:1 hexane–isopropanol mixture; flow rate, 1.0 ml/min; t_R of **11b**, 26.8 min; t_R of **12b**, 36.0 min]. **11b**: $[\alpha]_D^{20}$

–5.1 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 1736, 1695, 1417 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.85 (9H, s), 1.26 (3H, t, *J* = 7.2Hz), 1.54 (1H, ddd, *J* = 5.1. 9.8, 12.8 Hz), 2.02 (1H, dd, *J* = 5.2, 12.8 Hz), 2.41~2.66 (5H, m), 2.92 (1H, d, *J* = 12.2 Hz), 3.74 (1H, dd, *J* = 5.2, 12.2 Hz), 3.87 (1H, m), 4.14 (2H, *J* = 7.2 Hz), 4.56 (1H, m); FAB-HRMS calcd for $C_{17}H_{32}NO_4Si$ $(M+H)^+$: 342.2101. Found 342.2097. **12b**: $[\alpha]_D^{20}$ –41.0 (c 1.08, $CHCl_3$); IR (KBr) ν_{max} 1738, 1676, 1433 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.86 (9H, s), 1.26 (3H, t, *J* = 7.2 Hz), 1.43 (1H, ddd, *J* = 4.9, 11.1, 12.3 Hz), 1.68 (1H, dd, *J* = 5.2, 12.3 Hz), 2.11 (1H, dd, *J* = 4.2, 17.3 Hz), 2.29 (1H, dd, *J* = 7.6, 16.1 Hz), 2.42 (1H, dd, *J* = 7.6, 12.6 Hz), 2.88~3.05 (3H, m), 3.76 (1H, dd, *J* = 4.9, 12.1 Hz), 4.14 (2H, q, *J* = 7.2 Hz), 4.26 (1H, ddd, *J* = 5.2, 7.1, 11.1 Hz), 4.55 (1H, t, *J* = 4.9 Hz); FAB-HRMS calcd for $C_{17}H_{32}NO_4Si$ $(M+H)^+$: 342.2101. Found: 342.2121.

3-[(2S,4R)-*N*-Benzyloxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]glutaric acid 9f.

To a solution of **9e** (62.0 g, 119 mmol) in MeOH (400 ml) was added 1N aqueous NaOH solution (250 ml), and the mixture was stirred overnight at room temperature. The mixture was quenched by adding 1N HCl (250 ml) and was evaporated under reduced pressure. The residue was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification of the residue by silica gel column chromatography gave **9f** (46.6 g, 86%), $[\alpha]_D^{20}$ –32.4 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 1712, 1657 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.83 (9H, s), 1.71 (1H, m), 1.89 (1H, m), 2.08~2.54 (4H, m), 2.98~3.32 (2H, m), 3.68 (1H, m), 4.13 (1H, m), 4.31 (1H, br), 5.06~5.24 (2H, m), 7.23~7.43 (5H, m); FAB-MS *m/z* 466 $(M+H)^+$; Anal. Calcd for $C_{23}H_{35}NO_7Si$: C, 59.33; H, 7.58; N, 3.01. Found: C, 59.10; H, 7.75; N, 2.98.

(4S,5S,7R)-7-*tert*-Butyldimethylsilyloxy-4-carboxymethyl-2-oxo-1-azabicyclo[3,3,0]-octane 15.

To a solution of **9f** (14.2 g, 30.5 mmol) in THF (150 ml) was added dicyclohexylcarbodiimide (6.61 g, 32.0 mmol), and the mixture was stirred overnight at room temperature. The resulting precipitate was filtered off and washed with THF. The filtrate and washings were combined, and 10% Pd–C on carbon (4.5 g) was added to the solution. After the mixture was stirred for 6 hrs under a hydrogen atmosphere at room temperature, the catalyst was filtered off through a pad of celite and washed with THF. The combined filtrate and washings were evaporated under reduced pressure to give the residue, which was purified by silica gel column chromatography affording **15** (3.40 g, 94%), mp 127–129 °C (ether–heptane); $[\alpha]_D^{20}$ –38.6 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 1716, 1637, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.88 (9H, s), 1.57 (1H, *J* = 4.9, 9.8, 12.7 Hz), 2.06 (1H, dd, *J* = 5.4, 12.7 Hz), 2.45~2.60 (4H, m), 2.68 (1H, m), 2.95 (1H, d, *J* = 12.7 Hz), 3.75 (1H, dd, *J* = 5.4, 12.7 Hz), 3.92 (1H, dt, *J* = 6.4, 9.6 Hz), 4.58 (1H, m); ^{13}C NMR ($CDCl_3$) δ -5.01, -4.94, 17.87, 25.60, 37.54, 38.28, 41.13, 41.70, 51.28, 65.36, 74.01, 173.64, 175.27; FAB-MS *m/z* 314 $(M+H)^+$; Anal. Calcd for $C_{15}H_{27}NO_4Si \cdot 0.5H_2O$: C, 55.87; H, 8.75; N, 4.34. Found: C, 55.84; H, 8.73; N, 4.33.

(4S,5S,7R)-4-*tert*-Butoxycarbonylaminomethyl-7-*tert*-butyldimethylsilyloxy-2-oxo-1-azabicyclo[3,3,0]octane 8.

To a solution of **15** (500 mg, 1.60 mmol) in *tert*-BuOH (10 ml) were added triethylamine (0.23 ml, 1.65

mmol) and diphenylphosphorylazide (0.35 ml, 1.63 mmol) and the mixture was stirred for 23 hrs at reflux temperature. The mixture was allowed to cool to room temperature and concentrated under reduced pressure, and the residue was extracted with EtOAc. The organic layer was washed with 5% aqueous Na_2CO_3 and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to yield **8** (385 mg, 63% yield, >99% de), [HPLC analysis: column, Daicel CHIRALPAK AD; detection, 230 nm; eluent, 95:5 hexane–isopropanol mixture; flow rate, 1.5 ml/min; t_R of **8**, 5.4 min; t_R of **21**, 5.8 min]. mp 126–127 °C (heptane); $[\alpha]_D^{20}$ –40.2 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 1701, 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.88 (9H, s), 1.44~1.54 (10H, m), 2.00 (1H, dd, J = 5.4, 12.2 Hz), 2.32 (1H, m), 2.48 (2H, d, J = 9.8 Hz), 2.92 (1H, d, J = 12.2 Hz), 3.20~3.33 (2H, m), 3.75 (1H, dd, J = 5.4, 12.2 Hz), 3.92 (1H, ddd, J = 3.4, 5.9, 7.3 Hz), 4.57 (1H, m), 4.71 (1H, m); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ -5.01, -4.97, 17.87, 25.60, 28.24, 28.55, 38.92, 41.77, 42.90, 42.98, 51.17, 63.24, 74.07, 79.53, 155.72, 173.31; FAB-HRMS calcd for $C_{19}H_{37}N_2O_4Si$ $(M+H)^+$: 385.2522. Found 385.2542.

(2S,4R)-*N*-Benzyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(4S)-2-pyrrolidon-4-yl] pyrrolidine 18.

To an ice-cooled solution of **5** (1.0 g, 2.6 mmol) in CH_2Cl_2 (10 ml) was added TFA (5.0 ml) dropwise. After being stirred for 1 hr at 0 °C, the mixture was concentrated under reduced pressure. To the residue in CH_2Cl_2 (10.0 ml) was added triethylamine (3.3 ml, 23.4 mmol) and benzyl chloroformate (0.41 ml, 2.9 mmol) at 0 °C, and the mixture was stirred for 1 hr at the same temperature. After the mixture was concentrated under reduced pressure, the residue was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica column chromatography gave **18** (720 mg, 66%), IR (KBr) ν_{max} 1699, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.04 (3H, s), 0.84 (9H, s), 1.67~1.82 (1H, m), 1.92~2.24 (2H, m), 2.33~2.48 (1H, m), 2.95~3.25 (2H, m), 3.27~3.44 (2H, m), 3.57~3.80 (1H, m), 4.21 (1H, m), 4.32 (1H, m), 5.06~5.20 (2H, m), 7.26~7.42 (5H, m); FAB-MS *m/z* 419 $(M+H)^+$.

Methyl (3S)-3-[(2S, 4R)-*N*-benzyloxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-4-*tert*-butoxycarbonylaminobutyrate 19.

To a solution of **18** (580 mg, 1.4 mmol) in Ch_3CN (10 ml) was added di-*tert*-butyl dicarbonate (410 mg, mmol) and 4-dimethylaminopyridine (250 mg, 2.0 mmol). After being stirred for 5 hrs at room temperature, the mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with 5% aqeous citric acid and brine, dried over $MgSO_4$, and concentrated under reduced pressure. To a solution of the residue in MeOH (10 ml) was added MeONa (110 mg, 2.0 mmol), and the mixture was stirred for 1 hr at 0 °C. After the mixture was concentrated under reduced pressure, the residue was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification of the residue by silica gel column chromatography gave **19** (740 mg, 95%), IR (KBr) ν_{max} 1699, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (3H, s), 0.04 (3H, s), 0.83 (9H, s), 1.42 (9H, s), 1.78~1.90 (1H, m), 1.92~2.04 (2H, m), 2.18~2.54 (3H, m), 2.97~3.30 (3H, m), 3.53~3.70 (4H, m), 3.98~4.23 (1H, m), 4.33 (1H, brs), 5.01~5.20 (2H, m), 7.29~7.41 (5H, m); FAB-MS *m/z* 563 $(M+H)^+$.

(4S,5S,7R)-4-*tert*-Butoxycarbonylaminomethyl-7-*tert*-butyldimethylsilyloxy-2-oxo-1-azabicyclo[3,3,0]octane 8.

A mixture of **19** (700 mg, mmol) and 10% Pd-C (250 mg) in MeOH (10 ml) was stirred for 2 hrs under a hydrogen atmosphere. The mixture was passed through a pad of celite, and the filtrate was concentrated under reduced pressure. A solution of the residue in toluene (8 ml) was heated overnight at 80 °C. The mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by column chromatography gave **8** (340 mg, 71%), mp 127–129 °C (heptane); $[\alpha]_D^{20}$ –39.0 (c 1.0, $CHCl_3$). The IR and ^1H NMR spectra were identical to those of the compound **8** obtained above. The difference NOE experiments suggested that the stereochemical structure of **8** was elucidated to be depicted as shown in ref. 6.

(4R,5S,7R)-4-*tert*-Butoxycarbonylaminomethyl-7-*tert*-butyldimethylsilyloxy-2-oxo-1-azabicyclo[3,3,0]octane 21.

21 was prepared from **20**[4] as described for the preparation of **8** from **5**, mp 130–131 °C (heptane); $[\alpha]_D^{20}$ –45.2 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 1705, 1674, 1533 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.86 (9H, s), 1.43 (9H, s), 1.53 (1H, brdt, *J* = 12.2, 6.9 Hz), 1.73 (1H, dd, *J* = 12.2, 5.3 Hz), 2.15 (1H, dd, *J* = 16.8, 3.6 Hz), 2.67 (1H, m), 2.79 (1H, d, *J* = 16.8 Hz), 2.87 (1H, d, *J* = 12.5 Hz), 2.98 (1H, m), 3.23 (1H, m), 3.74 (1H, dd, *J* = 12.5, 5.0 Hz), 4.28 (1H, ddd, *J* = 6.9, 6.3, 5.3 Hz), 4.56 (1H, brt, *J* = 5.0 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -4.90, -4.85, 17.94, 25.86, 28.32, 34.07, 35.82, 38.06, 42.30, 51.54, 61.37, 73.62, 79.70, 155.69, 173.84; FAB-HRMS calcd for $C_{19}H_{37}N_2O_4Si$ $(M+H)^+$: 385.2522. Found 385.2542; Anal. Calcd for $C_{19}H_{36}N_2O_4Si \cdot 0.5H_2O$: C, 57.98; H, 7.12; N, 9.48. Found: C, 58.09; H, 7.18; N, 9.83. The NOESY experiments suggested that the stereochemical structure of **21** was elucidated to be depicted as shown in ref. 8.

(3S)-4-Amino-3-[(2S,4R)-4-hydroxypyrrolidin-2-yl]butyric acid·dihydrochloride 7a.

A mixture of **8** (1.0 g, 2.60 mmol) in conc. hydrochloric acid (15 ml) was stirred for 12 hrs at reflux temperature. The mixture was cooled to room temperature and concentrated under reduced pressure to yield the residue, which was crystallized from EtOH, affording **7a** (571 mg, 99%), mp 179–181 °C (EtOH); $[\alpha]_D^{20}$ –4.4 (c 1.0, H_2O); IR (KBr) ν_{max} 3400, 1716, 1616, 1417 cm^{-1}; ^1H NMR (300 MHz, D_2O) d 1.96 (1H, ddd, *J* = 4.3, 12.2, 13.6 Hz), 2.28 (1H, dd, *J* = 6.0, 13.6 Hz), 2.58 (1H, m), 2.76 (2H, d, *J* = 5.6 Hz), 3.13 (1H, dd, *J* = 8.8, 13.4 Hz), 3.21 (1H, dd, *J* = 6.0, 13.4 Hz), 3.30 (1H, d, *J* = 12.9 Hz), 3.54 (1H, dd, *J* = 4.3, 12.9 Hz), 3.95 (1H, ddd, *J* = 6.0, 9.2, 12.2 Hz), 4.65 (1H, brt, *J* = 4.3 Hz); FAB-MS *m/z* 189 $(M+H)^+$; Anal. Calcd for $C_8H_{16}N_2O_3 \cdot 2HCl$: C, 36.79; H, 6.95; N, 10.73. Found: C, 36.85; H, 6.93; N, 10.52.

(3S)-4-*tert*-Butoxycarbonylamino-3-[(2S,4R)-*N*-*tert*-butoxycarbonyl-4-hydroxypyrrolidin-2-yl]butyric acid 7b.

To a suspension of **7a** (571 mg, 2.19 mmol) and Na_2CO_3 (580 mg, 5.47 mmol) in a mixture of dioxane (15 ml) and H_2O (10 ml) was added di-*tert*-butyl dicarbonate (1.05 g, 4.81 mmol) and the mixture was stirred for 6 hrs at room temperature. The mixture was poured into EtOAc and the pH of the mixture was adjusted to 3.5 with 1N hydrochloric acid. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residual oil was purified by silica gel column chromatography to yield **7b** (770 mg, 91%), $[\alpha]_D^{20}$ –35.6 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 3361, 1691, 1408 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ

1.42 (9H, s), 1.46 (9H, s), 1.84~2.13 (2H, m), 2.26~2.53 (3H, m), 3.04 (1H, m), 3.20 (1H, m), 3.25 (1H, dd, J = 4.3, 12.2 Hz), 3.62 (1H, d, J = 12.2 Hz), 4.08 (1H, br), 4.40 (1H, br); FAB-HRMS calcd for $C_{18}H_{33}N_2O_7$ $(M+H)^+$: 389.2288. Found 389.2285.

(2S,4R)-*N*-*tert*-Butoxycarbonyl-[(3S)-*N*-*tert*-butoxycarbonylpyrrolidin-3-yl]-4-hydroxy pyrrolidine 16.

To a solution of **7b** (630 mg, 1.62 mmol) in THF (15 ml) was added $BH_3 \cdot SMe_2$ (0.57 ml, 5.7 mmol) at 40 °C and the mixture was stirred for 2 hrs at room temperature. The mixture was carefully quenched with MeOH (3.0 ml) and further stirred for 30 min until the gass evolution ceased. The mixture was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography to yield **16** (453mg, 78%), $[\alpha]_D^{20}$ –51.0 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 3477, 1691, 1408 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.47 (9H, s), 1.60~2.08 (4H, m), 2.49~2.68 (1H, m), 2.97 (1H, m), 3.23 (1H, m), 3.27~3.72 (4H, m), 4.10 (1H, m), 4.42 (1H, m); FAB-HRMS calcd for $C_{18}H_{33}N_2O_5$ $(M+H)^+$: 357.2389. Found 357.2389.

(2S,4R)-4-Hydroxy-2-[(3S)-pyrrolidin-3-yl]pyrrolidine·dihydrochloride 3.

To a solution of **16** (1.67 g, 4.69 mmol) in MeOH (20 ml) was added a 3.0 N hydrogen chloride in MeOH (6.0 ml) and the mixture was stirred for 6 hrs at room temperature. The mixture was evaporated under reduced pressure and the residue was crystallized from EtOH to produce **3** (1.16 g, 95%), mp 242~244 °C (dec.); $[\alpha]_D^{20}$ +1.2 (c 1.0, H_2O), {lit.[4] mp 240~242 °C (dec.); $[\alpha]_D^{20}$ +2.2 (c 1.0, H_2O)}; IR (KBr) ν_{max} 3327, 2895, 2735 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.81~1.96 (2H, m), 2.22 (1H, ddt, J = 1.4, 5.9, 13.9 Hz), 2.38 (1H, m), 2.69 (1H, dq, J = 8.0, 9.6 Hz), 3.05 (1H, dd, J = 9.6, 12.1 Hz) 3.30 (1H, dt, J = 1.5, 13.0 Hz) 3.35 (1H, ddd, J = 7.3, 9.5, 12.1 Hz), 3.47~3.61 (3H, m), 4.65 (1H, t, J = 4.3 Hz); FAB-MS *m/z* 189 $(M+H)^+$; Anal. Calcd for $C_8H_{16}N_2O \cdot 2HCl$: C, 41.93; H, 7.92; N, 12.22. Found: C, 41.87; H, 7.98; N, 12.17.

(2S,4S)-4-Acetylthio-N-*tert*-butoxycarbonyl-[(3S)-N-*tert*-butoxycarbonylpyrrolidin-3-yl]pyrrolidine 6a.

To a mixture of **16** (500 mg, 1.30 mmol) and triphenylphosphine (710 mg, 2.71 mmol) in THF (15 ml) was added diethyl azodicarboxylate (0.43 ml, 2.73 mmol) at 4 °C. After the mixture was stirred for 30 min at 4 °C, thioacetic acid (0.20 ml, 0.28 mmol) was added, and the resulting mixture was further stirred for 30 min at the same temperature. The mixture was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to yield **6a** (511 mg, 88%), $[\alpha]_D^{20}$ –7.3 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 1695, 1400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (9H, s), 1.54~1.80 (2H, m), 1.91 (1H, m), 2.39(3H, s), 2.39~2.75 (2H, m), 2.90~3.08 (2H, m), 3.21 (1H, m), 3.28~3.56 (2H, m), 3.86 (1H, m), 3.92~4.32 (2H, m); FAB-HRMS calcd for $C_{20}H_{35}N_2O_5S$ $(M+H)^+$: 415.2266. Found 415.2283.

Diethyl 3-[(2S)-N-benzyloxycarbonylpyrrolidin-2-yl]glutarate 22.

22 was prepared as described for the preparation of **9b**, $[\alpha]_D^{20}$ –41.0 (c 1.08, $CHCl_3$); IR (KBr) ν_{max} 1732, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12~1.30 (6H, m), 1.65~2.05 (4H, m), 2.15~2.63 (3H, m), 2.87 (1H, m), 3.23 (2H, m), 3.90~4.25 (6H, m), 5.03~5.23 (2H, m), 7.28~7.50 (5H, m); FAB-HRMS calcd for $C_{21}H_{30}NO_6$ $(M+H)^+$: 392.2085. Found: 392.2079.

(4S,5S)-4-Carboxymethyl-2-oxo-1-azabicyclo[3,3,0]octane 25.

25 was prepapred from **23** using the above procedure for the preparation of **15**, $[\alpha]_D^{20}$ –6.3 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 1701, 1659, 1446 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (1H, m), 1.95~2.20 (3H, m), 2.45~2.65 (4H, m), 2.72 (1H, m), 3.07 (1H, m), 3.50~3.70 (2H, m); FAB-MS *m/z* 184 $(M+H)^+$.

(4S,5S)-4-Ethoxycarbonylmethyl-2-oxo-1-azabicyclo[3,3,0]octane 26.

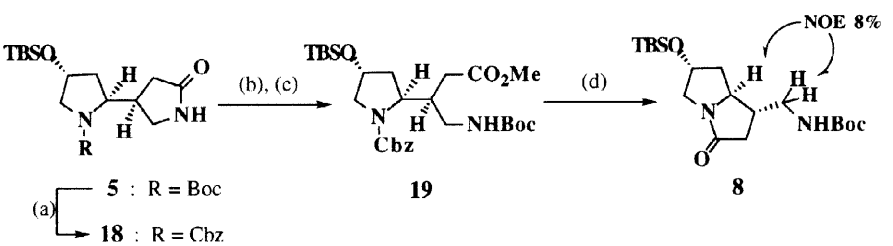
To a solution of **25** (200 mg, 1.1 mmol) in DMF (5.0 ml) was added potassium carbonate (151 mg, 1.1 mmol) and iodoethane (0.17 ml, 2.1 mmol) and the mixture was stirred for 3 hrs at room temperature. The mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification of the residue by silica gel column chromatography yielded **24** (184 mg, 80 % yield, 97% de), [HPLC analysis: column, YMCgel ODS-AQ 120-S50; detection, 210 nm; eluent, 30:70 CH_3CN–H_2O mixture; flow rate, 1.0 ml/min; t_R of **26**, 4.7 min; t_R of the diastereomer of **26**, 4.2 min], $[\alpha]_D^{20}$ –41.2 (c 0.62, EtOH), [lit.[14] $[\alpha]_D^{20}$ –35.8 (c 0.6, EtOH)]; IR (KBr) ν_{max} 1730, 1678, 1423 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (3H, t, *J* = 7.0 Hz), 1.41~1.52 (1H, m), 1.95~2.17 (3H, m), 2.45~2.72 (5H, m), 3.05 (1H, ddd, *J* = 3.7, 8.8, 12.0 Hz), 3.50~3.65 (2H, m), 4.14 (2H, q, *J* = 7.0 Hz); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 14.06, 26.72, 31.27, 38.09, 38.46, 41.09, 41.53, 60.60, 67.13, 171.50, 173.13; FAB-HRMS calcd for $C_{11}H_{18}NO_3$ $(M+H)^+$: 212.1287. Found: 212.1279.

Acknowledgement

The authors would like thank Ms. Chihiro Suzuki and Ms. Ikuko Anma for technical assistance.

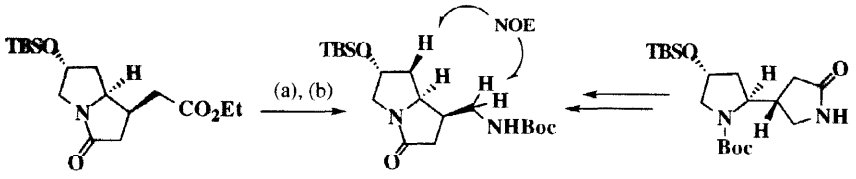
References and notes

1. Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, M.; Monchales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiotics* **1979**, *32*, 1.
2. Shih, D. H.; Baker, F.; Cama, L.; Christensen, B.G. *Heterocycles* **1984**, *21*, 29.
3. Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiotics* **1990**, *43*, 519.
4. Ohtake, N.; Yamada, K.; Mano, E.; Okamoto O.; Ushijima, R.; Nakagawa, S. *J. Antibiotics* **1997**, *50*, 567.
5. Leanza, W. J.; Wildonger, K. J.; Miller, T. W.; Christensen, B. G. *J. Med. Chem.* **1979**, *22*, 1435.
6. The stereochemical structure of the pyrrolidin-3-yl moiety of **2** was elucidated by NOE experiments of **8**, which was derived from **5** in the following steps.



Reagents : (a) TFA, CH_2Cl_2, 0°C, then CbzCl, NEt_3, (b) Boc_2O, DMAP, CH_3CN, r. t., (c) NaOMe, MeOH, 0°C, (d) 10% Pd-C, r. t..

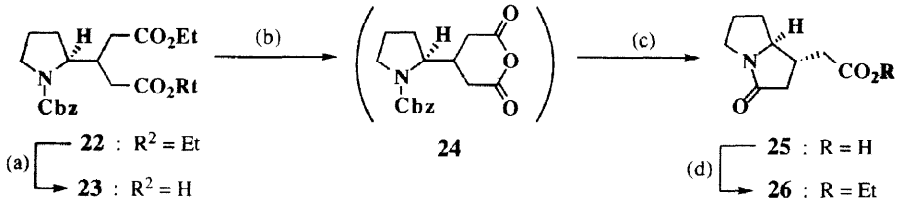
7. Krapcho, A. P.; Loveu, A. J. *Tetrahedron Lett.* **1973**, 957.
8. The stereochemical structures of **11b** and **12b** were determined after conversion of **11b** and **12b** to **8** and **21**, respectively, by the following method. Compound **21** was derived from **20**[4] by a similar method described above, and its stereochemical structure was elucidated by NOESY experiments.



12b 21 20

Reagents : (a) 1N NaOH, MeOH, r. t., (b) $(PhO)_2PON_3$, NEt_3, *tert*-BuOH, 70 °C.

9. Basha, A.; Lipton, M.; Weinreb, S. M. *Terahedron Lett.* **1977**, 4171.
10. The diastereoselectivity was determined after conversion to the corresponding ethyl esters (**11b** and **12b**) by HPLC {YMC A-001 (S-5, 120A SIL)}.
11. This method was applied to the diastereoselective synthesis of **24** (97% de), which had been employed as a key intermediate for the (-)-trachelanthamidine synthesis.[14]



Reagents: (a) 1N NaOH, EtOH, (b) DCC, THF, (c) 10% Pd-C, H_2, THF, (d) EtI, K_2CO_3, DMF.

12. Ninomiya, K.; Shoiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.
13. Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.
14. Sato, T.; Tsujimoto, K.; Matsubayashi, K.; Ishibashi, H.; Ikeda, M. *Chem. Pharm. Bull.* **1992**, *40*, 2308.